

### ELECTION

The Examiner has required restriction between:

1. Claims 1-21, drawn to a parental formulation.
2. Claims 22-30, drawn to a freeze-dried formulation.
3. Claims 31-36, drawn to a parental formulation that comprises an aqueous solvent and a freeze-dried formulation.
4. Claims 37-39, drawn to a process for preparing a parental formulation.
5. Claims 40-42, drawn to a process for preparing a freeze-dried formulation.
6. Claims 43-45, drawn to a process for preparing a freeze-dried formulation.
7. Claim 46, drawn to a formulation that comprises an aqueous solvent and a freeze-dried formulation.
8. Claims 47 and 49, drawn to a parental formulation which does not contain any water.
9. Claims 47-49, drawn to a parental formulation which does contain water.
10. Claim 50, drawn to a method of using the formulation of claim 1.
11. Claim 51, drawn to a method of using the formulation of claim 31.
12. Claim 52, drawn to a method of using the formulation of claim 46.

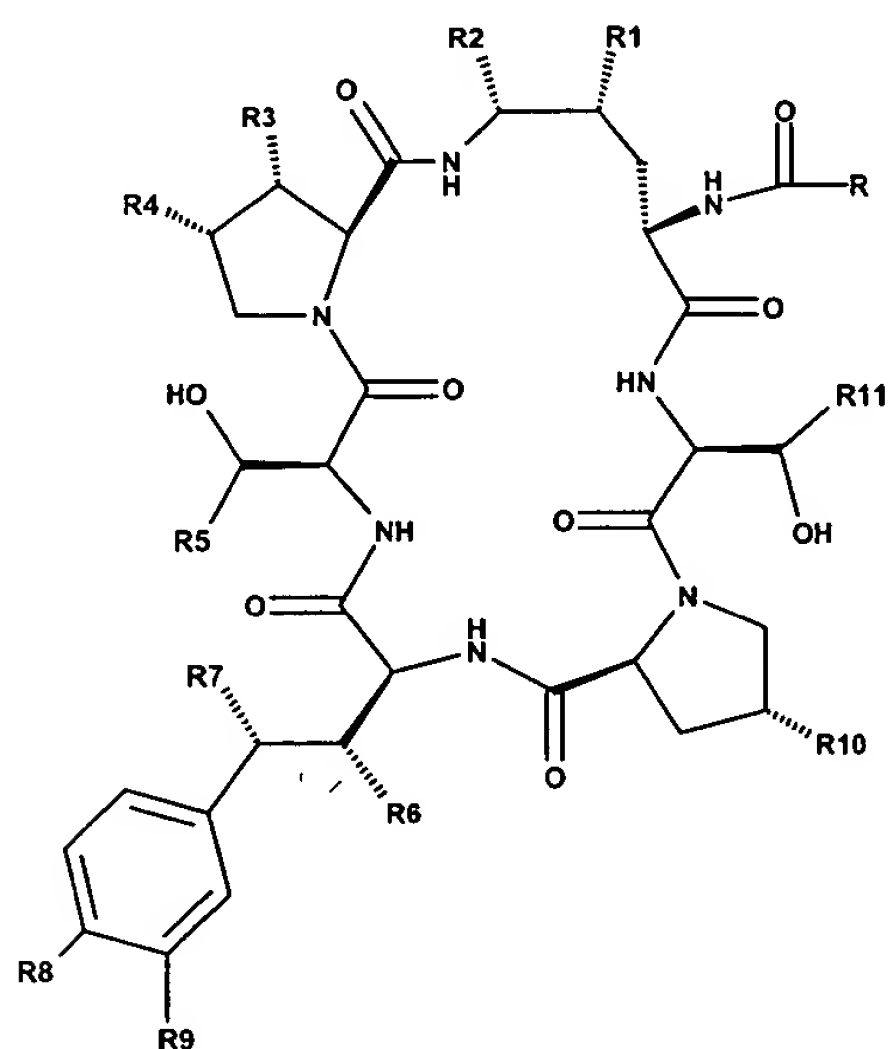
Applicant hereby elects Group 2, without traverse.

Applicant expressly reserves his/her right under 35 U.S.C. § 121 to file a divisional application directed to the non-elected subject matter during the pendency of this application, or an application claiming priority from this application. Applicant further notes that upon indication of allowable subject matter of the claims of Group 2 (formulations), claims directed to methods of making such formulations will be rejoined for further examination (§MPEP 821.04). The Applicant

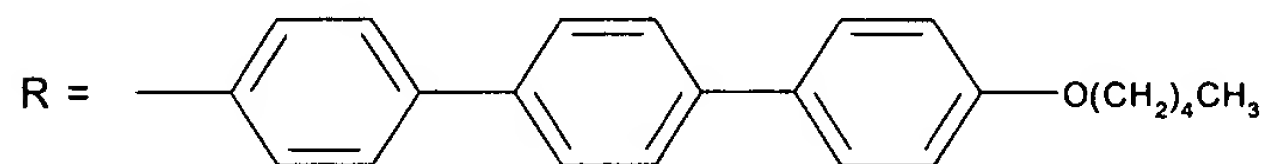
notes that the Examiner has also stated that additional rejoinder may also be considered when the novelty and non-obviousness of the claimed subject matter has been agreed upon.

The Examiner also has requested an election of species under 35 U.S.C. § 1.121. The Applicant hereby elects the species where

1. The echinocandin is represented by the formula shown below:



where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^6$ ,  $R^7$ ,  $R^8$ , and  $R^{10}$  are hydroxy groups;  $R^4$ ,  $R^5$  and  $R^{11}$  are methyl groups;  $R^9$  is a hydrogen, and R is defined as:



2. The surfactant is a polysorbate. If a particular polysorbate is required, the Applicant elects polysorbate 80.

3. The bulking agent is mannitol.

4. The concentration of surfactant is 26% (w/w). (see Table 4, last line of page 29). We note that the Examiner has requested the election of a “concentration” of surfactant, a term usually used to refer to weight/volume, but in the restriction requirement referred to the limitation of claim 22 (“in an amount greater than 5% (w/w).”) as a surfactant “concentration”. If, rather than the (w/w) amount the Examiner was indeed referring to a mg/ml “concentration”, then the Applicants would instead elect 25 mg/ml.

Claims readable on the above election of species include claims 22-30.

Applicant requests examination of the elected subject matter on the merits. The Applicant notes that the generic claims should be considered if one or more species claims are found patentable.

## AMENDMENTS

### **In the claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

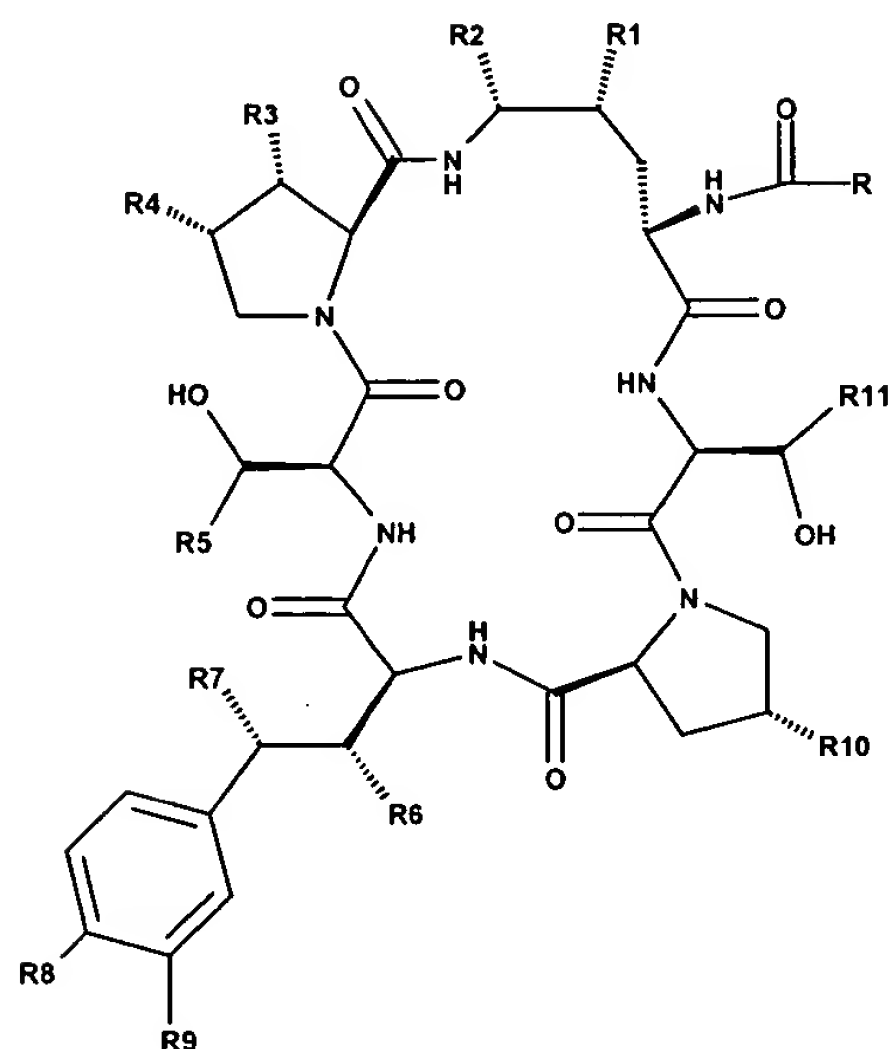
### **Listing of Claims:**

Claim 1 (withdrawn): A parenteral pharmaceutical formulation comprising

- (i) an echinocandin compound, or a pharmaceutically acceptable salt thereof;
- (ii) a pharmaceutically acceptable micelle-forming surfactant; and
- (iii) a non-toxic, aqueous solvent

wherein said surfactant is present in said formulation at a weight ratio of echinocandin compound to micelle-forming surfactant from about 1:1.75 to about 1:25 and said echinocandin compound is present in an amount greater than or equal to 1 mg/ml.

Claim 2 (withdrawn): The formulation of Claim 1 wherein said echinocandin compound is represented by the following structure:



wherein:

R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, heteroaryl group, or combinations thereof;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, and R<sub>10</sub> are independently hydroxy or hydrogen;

R<sub>4</sub> is hydrogen, methyl or -CH<sub>2</sub>C(O)NH<sub>2</sub>;

R<sub>5</sub> and R<sub>11</sub> are independently methyl or hydrogen;

R<sub>8</sub> is -OH, -OPO<sub>3</sub>H<sub>2</sub>, -OPO<sub>3</sub>HCH<sub>3</sub>, -OPO<sub>2</sub>HCH<sub>3</sub>, or -OSO<sub>3</sub>H;

R<sub>9</sub> is -H, -OH, or -OSO<sub>3</sub>H; and

pharmaceutically acceptable salts thereof.

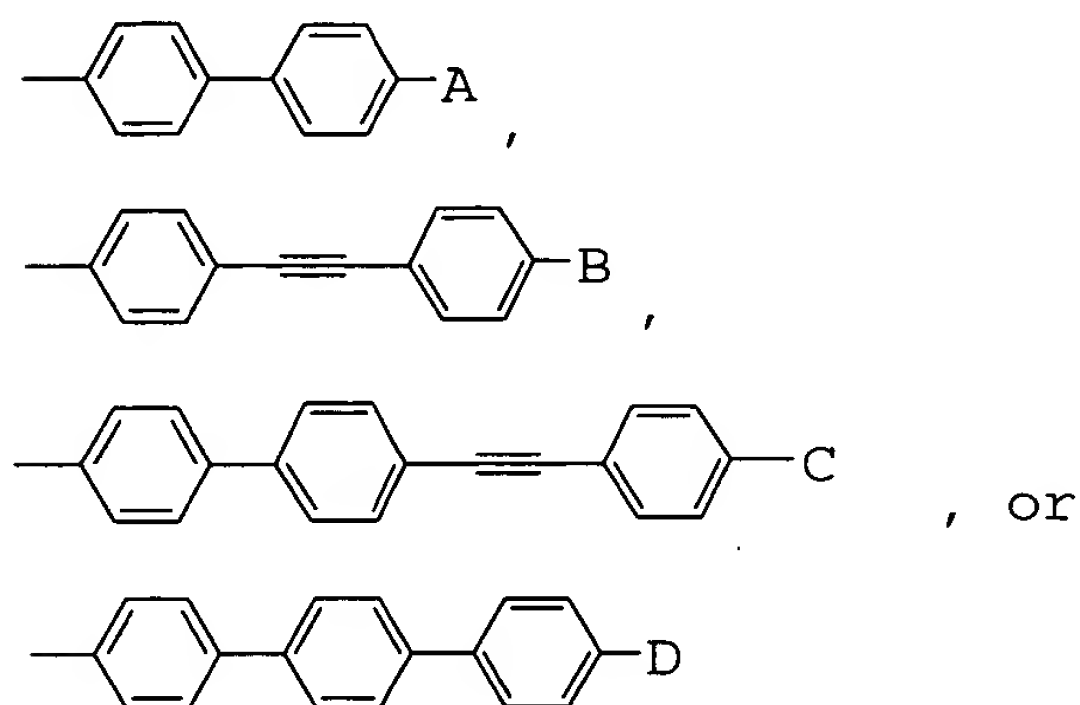
Claim 3 (withdrawn): The formulation of Claim 2 wherein

R<sub>4</sub>, R<sub>5</sub> and R<sub>11</sub> are each methyl;

R<sub>2</sub> and R<sub>7</sub> are independently hydrogen or hydroxy; R<sub>1</sub>, R<sub>3</sub>, R<sub>6</sub> and R<sub>10</sub> are each hydroxy;

$R_8$  is -OH, -OPO<sub>3</sub>HCH<sub>3</sub>, or -OPO<sub>2</sub>HCH<sub>3</sub>;

R is linoleoyl, palmitoyl, stearoyl, myristoyl, 12-methylmyristoyl, 10,12-dimethylmyristoyl, or a group having the general structure:



where A, B, C and D are independently hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>2</sub>-C<sub>12</sub> alkynyl, C<sub>1</sub>-C<sub>12</sub> alkoxy, C<sub>1</sub>-C<sub>12</sub> alkylthio, halo, or -O-(CH<sub>2</sub>)<sub>m</sub>-[O-(CH<sub>2</sub>)<sub>n</sub>]<sub>p</sub>-O-(C<sub>1</sub>-C<sub>12</sub> alkyl) or -O-(CH<sub>2</sub>)<sub>q</sub>-X-E;

m is 2, 3 or 4;

n is 2, 3 or 4; p is 0 or 1; q is 2, 3 or 4;

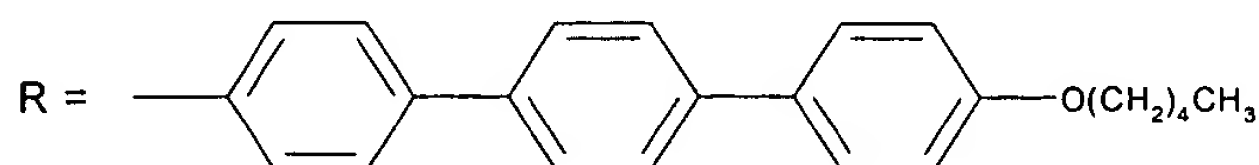
X is pyrrolidino, piperidino or piperazino;

E is hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>3</sub>-C<sub>12</sub> cycloalkyl, benzyl or C<sub>3</sub>-C<sub>12</sub> cycloalkylmethyl.

Claim 4 (withdrawn): The formulation of claim 3 wherein

$R_2$  and  $R_7$  are each hydroxy;

$R_8$  is hydroxy; and

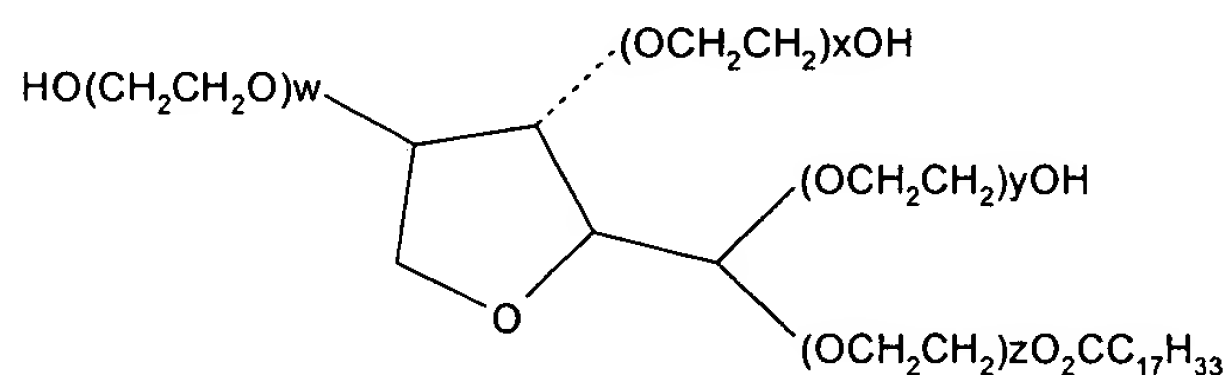


Claim 5 (withdrawn): The formulation of Claim 1 wherein said micelle-forming surfactant is selected from the group consisting of polysorbates, polyoxyethylene castor oil derivatives, polyoxyethylene stearates, sorbitan trioleate, bile salts, lecithin and combinations thereof.

Claim 6 (withdrawn): The formulation of Claim 1 wherein said echinocandin compound is present in an amount from about 1 mg/ml to about 50 mg/ml.

Claim 7 (withdrawn): The formulation of Claim 6 wherein said echinocandin compound is present in an amount from about 1 to about 30 mg/ml.

Claim 8 (withdrawn): The formulation of Claim 1 wherein said surfactant is represented by the following formula:



wherein  $x+y+z+w$  is equal to an integer between 5 and 20.

Claim 9 (withdrawn): The formulation of Claim 1 wherein said surfactant is present in an amount greater than 1% weight per volume.

Claim 10 (withdrawn): The formulation of Claim 1 wherein said weight ratio of echinocandin to surfactant is from about 1:2 to about 1:3.

Claim 11 (withdrawn): The formulation of Claim 1 wherein said solvent is selected from the group consisting of water, ethanol, propylene glycol, polyethylene glycols and mixtures thereof.

Claim 12 (withdrawn): The formulation of Claim 1 further comprising a stabilizing agent.

Claim 13 (withdrawn): The formulation of Claim 12 wherein said stabilizing agent is present in an amount from about 0.5% to about 10% by weight per volume.

Claim 14 (withdrawn): The formulation of Claim 12 wherein said stabilizing agent is present in an amount from about 1% to about 6% by weight per volume.

Claim 15 (withdrawn): The formulation of Claim 12 wherein said stabilizing agent is selected from the group consisting of mannitol, histidine, lysine, glycine, sucrose, fructose, trehalose, lactose and mixtures thereof.

Claim 16 (withdrawn): The formulation of Claim 1 further comprising a buffer.

Claim 17 (withdrawn): The formulation of Claim 16 wherein said buffer is selected from the group consisting of acetates, citrates, tartrates, lactates, succinates and phosphates and amino acids.

Claim 18 (withdrawn): The formulation of Claim 1 further comprising a tonicity agent.

Claim 19 (withdrawn): The formulation of Claim 18 wherein said tonicity agent is selected from the group consisting of glycerin, lactose, mannitol, dextrose, sodium chloride, sodium sulfate and sorbitol.

Claim 20 (withdrawn): The formulation of Claim 18 wherein said tonicity agent is present in amount from about 1 to about 100 mg/ml.

Claim 21 (withdrawn): The formulation of Claim 18 wherein said tonicity agent is present in amount from about 9 to 50 mg/ml.

Claim 22 (original): A freeze-dried formulation comprising

(i) an echinocandin compound, or a pharmaceutically acceptable salt thereof;

(ii) a pharmaceutically acceptable micelle-forming surfactant; and

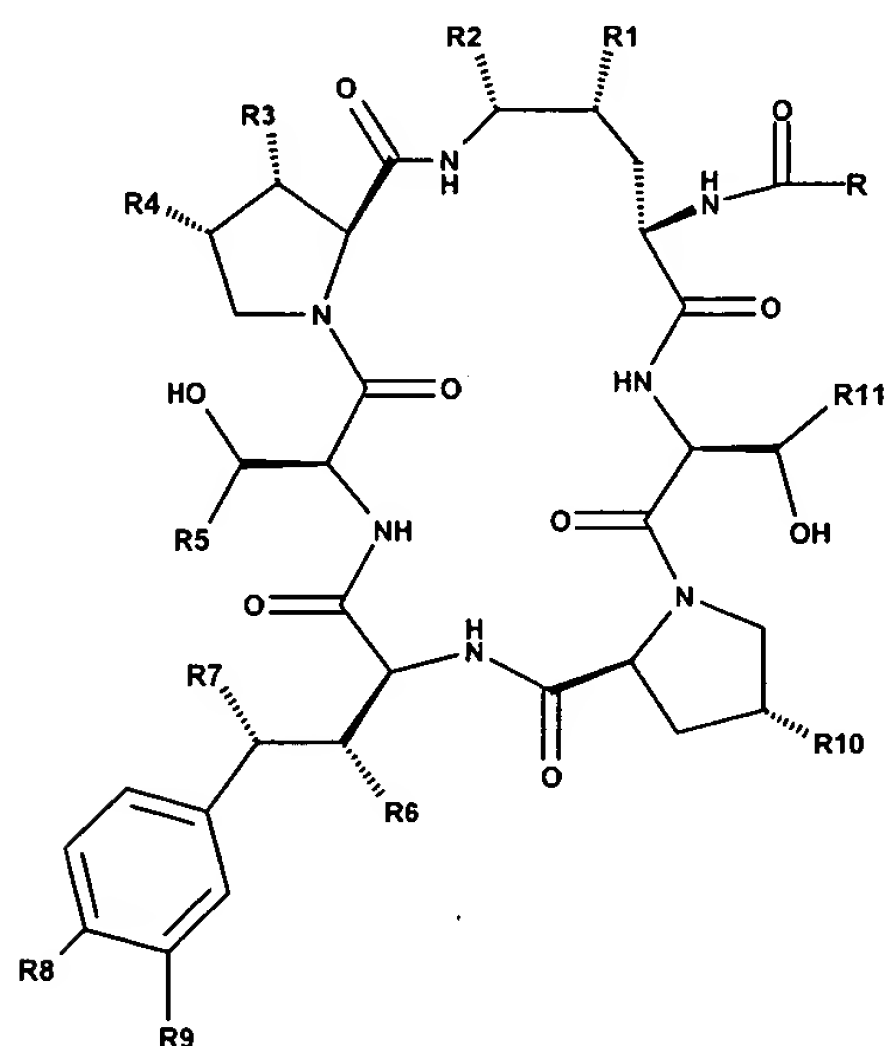


(iii) a bulking agent,

wherein said micelle-forming surfactant is present in said freeze-dried formulation in an amount greater than 5% by weight.

Claim 23 (original): The formulation of Claim 22 wherein said bulking agent is selected from the group consisting of mannitol, sucrose, trehalose, lactose and mixtures thereof.

Claim 24 (original): The formulation of claim 22 wherein said echinocandin compound is represented by the following structure:



wherein:

R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, heteroaryl group, or combinations thereof;

R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>6</sub>, R<sub>7</sub>, and R<sub>10</sub> are independently hydroxy or hydrogen;

R<sub>4</sub> is hydrogen, methyl or -CH<sub>2</sub>C(O)NH<sub>2</sub>;

R<sub>5</sub> and R<sub>11</sub> are independently methyl or hydrogen;

$R_8$  is -OH, -OPO<sub>3</sub>H<sub>2</sub>, -OPO<sub>3</sub>HCH<sub>3</sub>, -OPO<sub>2</sub>HCH<sub>3</sub>, or -OSO<sub>3</sub>H;

$R_9$  is -H, -OH, or -OSO<sub>3</sub>H; and

pharmaceutically acceptable salts thereof.

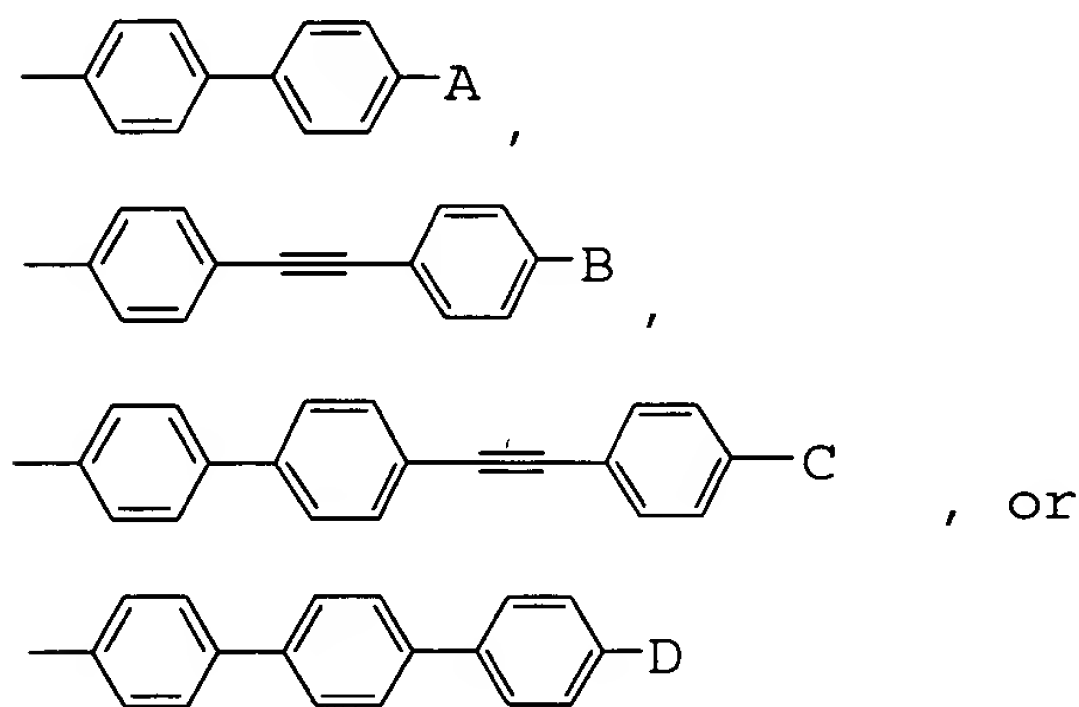
Claim 25 (original): The formulation of claim 24 wherein

$R_4$ ,  $R_5$  and  $R_{11}$  are each methyl;

$R_2$  and  $R_7$  are independently hydrogen or hydroxy;  $R_1$ ,  $R_3$ ,  $R_6$  and  $R_{10}$  are each hydroxy;

$R_8$  is -OH, -OPO<sub>3</sub>HCH<sub>3</sub>, or -OPO<sub>2</sub>HCH<sub>3</sub>;

$R$  is linoleoyl, palmitoyl, stearoyl, myristoyl, 12-methylmyristoyl, 10,12-dimethylmyristoyl, or a group having the general structure:



where A, B, C and D are independently hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>2</sub>-C<sub>12</sub> alkynyl, C<sub>1</sub>-C<sub>12</sub> alkoxy, C<sub>1</sub>-C<sub>12</sub> alkylthio, halo, or -O-(CH<sub>2</sub>)<sub>m</sub>-[O-(CH<sub>2</sub>)<sub>n</sub>]<sub>p</sub>-O-(C<sub>1</sub>-C<sub>12</sub> alkyl) or -O-(CH<sub>2</sub>)<sub>q</sub>-X-E;

$m$  is 2, 3 or 4;

$n$  is 2, 3 or 4;  $p$  is 0 or 1;  $q$  is 2, 3 or 4;

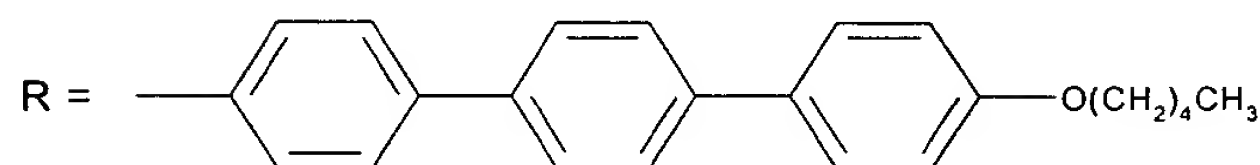
X is pyrrolidino, piperidino or piperazino;

E is hydrogen, C<sub>1</sub>-C<sub>12</sub> alkyl, C<sub>3</sub>-C<sub>12</sub> cycloalkyl, benzyl or C<sub>3</sub>-C<sub>12</sub> cycloalkylmethyl.

Claim 26 (original): The formulation of Claim 25 wherein

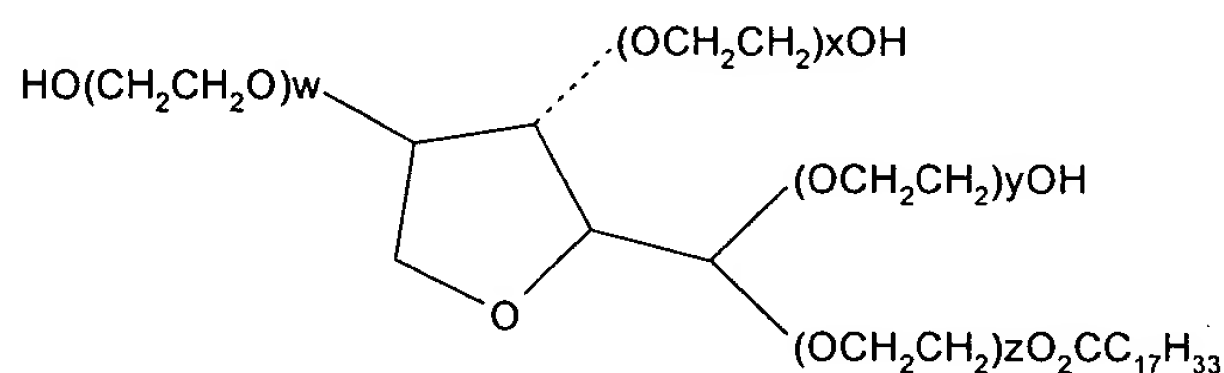
$R_2$  and  $R_7$  are each hydroxy;

$R_8$  is hydroxy; and



Claim 27 (original): The formulation of Claim 22 wherein said micelle-forming surfactant is selected from the group consisting of polysorbates, polyoxyethylene castor oil derivatives, polyoxyethylene stearates, sorbitan trioleate, bile salts, lecithin and combinations thereof.

Claim 28 (original): The formulation of Claim 22 wherein said surfactant is represented by the following formula:



wherein  $x+y+z+w$  is equal to an integer between 5 and 20.

Claim 29 (original): The formulation of Claim 22 wherein said surfactant is present in said formulation at a weight ratio of echinocandin to surfactant from about 1:1.75 to about 1:25.

Claim 30 (original): The formulation of Claim 29 wherein said weight ratio of echinocandin to surfactant is from about 1:2 to about 1:3.

Claim 31 (withdrawn): A parenteral formulation comprising the freeze-dried formulation of Claim 22 and an aqueous solvent.

Claim 32 (withdrawn): The formulation of Claim 31 further comprising a stabilizing agent.

Claim 33 (withdrawn): The formulation of Claim 32 wherein said stabilizing agent is selected from the group consisting of mannitol, histidine, lysine, glycine, fructose, sucrose, trehalose, lactose and mixtures thereof.

Claim 34 (withdrawn): The formulation of Claim 31 wherein said surfactant is present in said formulation at a weight ratio of echinocandin to surfactant from about 1:1.75 to about 1:25.

Claim 35 (withdrawn): The formulation of Claim 31 further comprising a buffer.

Claim 36 (withdrawn): The formulation of claim 35 wherein said buffer is selected from the group consisting of acetates, tartrates, citrates, phosphates and amino acids.

Claim 37 (withdrawn): A process for preparing a parenteral formulation comprising the step of mixing an echinocandin compound or an echinocandin/carbohydrate complex containing said echinocandin compound and a pharmaceutically acceptable micelle-forming surfactant in an aqueous solvent, wherein said micelle-forming surfactant is present in said formulation at a weight ratio of echinocandin compound to surfactant from about 1:1.75 to about 1:25 and said echinocandin compound is present in an amount greater than or equal to 1 mg/ml.

Claim 38 (withdrawn): The process of Claim 37 wherein said echinocandin compound is present in amount from about 1 mg/ml to about 50 mg/ml.

Claim 39 (withdrawn): The process of Claim 37 wherein said echinocandin compound is present in an amount from about 1 mg/ml to about 30 mg/ml.

Claim 40 (withdrawn): A process for making a freeze-dried formulation comprising in the following order the steps of:

(i) dissolving into an aqueous solvent an echinocandin compound or echinocandin/carbohydrate complex containing said echinocandin compound in the presence of a pharmaceutically acceptable micelle-forming surfactant to form a solution, wherein said surfactant is present in an amount greater than 1% weight per volume of solution;

(ii) sterile filtering said solution; and

(iii) freeze-drying said solution.

Claim 41 (withdrawn): The process of Claim 40 further comprising the step of adding one or more bulking agents, buffers, stabilizing agents, tonicity agents, or combinations thereof before step (ii).

Claim 42 (withdrawn): The process of Claim 40 wherein said micelle-forming surfactant is selected from the group consisting of polysorbates, polyoxyethylene castor oil derivatives, polyoxyethylene stearates, sorbitan trioleate, bile salts, lecithin and combinations thereof.

Claim 43 (withdrawn): A process for preparing a freeze-dried formulation comprising the steps of

(i) buffering a non-toxic aqueous solvent to a pH between 4.0 and 5.5 to form a buffered solution;

(ii) adding to said buffered solution a pharmaceutically acceptable, micelle-forming surfactant;

(iii) cooling the solution from step (ii) to a temperature between 5° and 15°C to form a cooled solution;

(iv) adding a slurry comprising an echinocandin compound or echinocandin/carbohydrate complex and a second non-toxic aqueous solvent to said cooled solution;

(v) sterile filtering said solution from step (iv); and

(vi) freeze-drying said solution from step (v).

Claim 44 (withdrawn): The process of Claim 43 wherein said temperature in step (iii) is from about 7°C to about 10°C.

Claim 45 (withdrawn): The process of Claim 43 further comprising the step of adding one or more bulking agents, stabilizing agents, tonicity agents, or combinations thereof before step (v).

Claim 46 (withdrawn): A parenteral formulation comprising an aqueous solvent and a freeze-dried formulation prepared by the process of Claim 43.

Claim 47 (withdrawn): A parenteral pharmaceutical product prepared by (i) dissolving into an aqueous solvent an echinocandin compound or echinocandin/carbohydrate complex containing said echinocandin compound in the presence of a pharmaceutically acceptable micelle-forming surfactant to form a solution, wherein said surfactant is present in an amount greater than 1% weight per volume of solution; (ii) sterile filtering said solution; and (iii) freeze-drying said solution from step (ii) in a vial.

Claim 48 (withdrawn): The product of Claim 47 wherein the preparation of said product further comprising adding a non-toxic, aqueous solvent to said vial after step (iii).

Claim 49 (withdrawn): The product of Claim 47 wherein the weight ratio of echinocandin compound to surfactant is from about 1:1.75 to about 1:25.

Claim 50 (withdrawn): A method of treating an antifungal infection in a mammal in need thereof comprising the step of administering to said mammal a parenteral formulation of Claim 1.

Claim 51 (withdrawn): A method of treating an antifungal infection in a mammal in need thereof comprising the step of administering to said mammal a parenteral formulation of Claim 31.

Claim 52 (withdrawn): A method of treating an antifungal infection in a mammal in need thereof comprising the step of administering to said mammal a parenteral formulation of Claim 46.

Claim 53 (new): The formulation of Claim 22 further comprising a stabilizing agent.

Claim 54 (new): The formulation of Claim 53 wherein said stabilizing agent is present in an amount from about 0.5% to about 10% by weight per volume.

Claim 55 (new): The formulation of Claim 53 wherein said stabilizing agent is present in an amount from about 1% to about 6% by weight per volume.

Claim 56 (new): The formulation of Claim 53 wherein said stabilizing agent is selected from the group consisting of mannitol, histidine, lysine, glycine, sucrose, fructose, trehalose, lactose and mixtures thereof.

Claim 57 (new): The formulation of Claim 22 further comprising a buffer.

Claim 58 (new): The formulation of Claim 57 wherein said buffer is selected from the group consisting of acetates, citrates, tartrates, lactates, succinates and phosphates and amino acids.

Claim 59 (new): The formulation of Claim 53, wherein the stabilizing agent is a polyol.

Claim 60 (new): The formulation of Claim 23, wherein said micelle-forming surfactant is selected from the group consisting of polysorbates, polyoxyethylene castor oil derivatives, polyoxyethylene stearates, sorbitan trioleate, bile salts, lecithin and combinations thereof. .

Claim 61 (new): The formulation of Claims 60, wherein said bulking agent is mannitol.

Claim 62 (new): The formulation of claim 56, further comprising a buffer and,  
wherein said stabilizing agent is fructose, said bulking agent is mannitol, and said micelle forming surfactant is a polysorbate.